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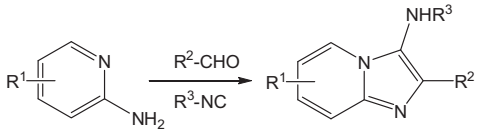
1. Current literature highlights

1.1. Combinatorial discovery of Fluorescent Pharmacophores

Labelling molecules with fluorescent labels is an important method for the study of a compound's function within cells. Although such fluorophores can be small in size, their addition to drug molecules can perturb the affinity of the tracked molecule for the target protein, thereby distorting the conclusions of any study. One way to circumvent this interference would be to discover ligands for important protein targets that are themselves fluorescent. To this end a recent publication describes a parallel synthetic approach to the discovery of fluorescent pharmacophores.[1]

Imidazo[1,2-*a*]pyridines are naturally occurring compounds that also possess pharmacological activity. Furthermore, they have intrinsic fluorescent properties. The imidazo[1,2-*a*]pyridine structure (**1**) can be generated by a three-component Ugi reaction (3-CR) of aromatic amidines with aldehydes and isocyanides. This reaction was used to generate an array of different compounds to permit the search for fluorophores with fluorescence in the visible region.



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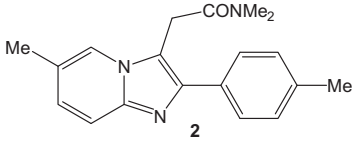
3-CRs were set up in 100 nL droplets aligned in a 800 spot microarray on a hydrophobic surface glass slide. Each 1:1 DMSO/water spot contained a different combination of amidines and aldehyde, and volatile isocyanides could be added by adsorption from the gas phase. Scandium triflate was used as the Lewis acid catalyst and reaction validation demonstrated at least 10% conversion to the aminoimidazo[1,2-*a*]pyridines – sufficient to detect the formation of fluorescent compounds.

To identify new fluorophores, 1600 unique combinations of product were generated from eight heterocyclic amidines, 40 aldehydes and five isocyanides. After completion of the chemistry, fluorescence was measured by a microarray scanner at four different filter settings. It was found that a number of amidines produced compounds that fluoresced with different colours, and using these amidines another library of 60 compounds was generated. The products were called 'Flugis' as an abbreviation of Fluorescent Ugi products. Some of the best Flugis in this library had extinction coefficients in the range $1.1–2.7 \times 10^4\ M^{-1}\ cm^{-1}$, and quantum yields in the range 0.2–0.9, giving fluorophore brightnesses B of $\sim 10^4\ M^{-1}\ cm^{-1}$, comparable to many commercial dyes.

Using this approach, a fluorescent ligand for one of the recognised targets of imidazo[1,2-*a*]pyridines was developed. Zolpidem (**2**) and analogues bind to the $GABA_A$ benzodiazepine receptor as well as the peripheral benzodiazepine receptor known as the translocator protein (TSPO). A collection of zolpidem analogues were prepared using 3-CR, and these were examined for their localisation in PC-3 prostate carcinoma cells. Of the compounds made, one compound (**3**), had a localisation that closely matched mitochondrial distribution. Incubation of cells with PK11195, a highly specific TSPO ligand was shown to significant displace fluorescent staining, confirming that **3** is also a TSPO ligand.



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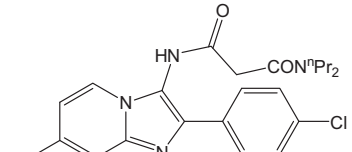

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This study demonstrates that a parallel synthetic approach is valuable in the discovery of autofluorescing drug-like molecules as bioimaging probes.

2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

A synthetic method for making lactic acid oligomers *via* solid-phase synthesis under mild reaction conditions with up to 99% yield has been presented. The fine control of the chirality on each lactic acid unit of the oligomers was easily achieved, and the overall synthesis of the trimer and tetramer was completed in

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one and two days respectively. Intramolecular cyclisations of enantio-controlled lactic acids were also attempted through the Yamaguchi macrolactonisation or the Mitsunobu reaction.[2]

2.2. Solution-phase synthesis

A library of pyridines and pyrimidines has been synthesised in excellent yields employing microwave and flow chemistry methodologies. Work-up bottlenecks have been circumvented by the use of supported reagents, and many of the final compounds have been studied in the solid state by single crystal X-ray diffraction.[3]

2.3. Scaffolds and synthons for combinatorial libraries

A practical and rapid preparation of 3-benzyloxy-4-bromo and 3-benzyloxy-5-bromopicolinate esters has been developed in four steps. Their viability as partners for cross-coupling reactions has been evaluated in Suzuki–Miyaura, Hartwig–Buchwald, and Sonogashira reactions to allow the synthesis of biologically relevant targets. The preparation of these two highly functionalisable scaffolds has not been described to date in the literature and could be used as common building blocks for the preparation of several biologically active compounds or agrochemical products.[4]

2.4. Solid-phase supported reagents

Non-cross-linked polystyrene-supported (carbomethoxymethyl)triphenylarsonium bromide and benzyltriphenylarsonium iodide have been synthesised. They have shown similar reactivities compared with the free arsonium salts for the arsa-Wittig reaction. The use of the polymer-supported reagents facilitated product purification and rendered the organoarsenic reagents easily separable and recyclable.[5]

2.5. Novel resins, linkers and techniques

2-Aminoethanol has been used to successively replace hydrazine in the preparation of aminomethyl polystyrene resin thereby facilitating purification and by-product removal. The syntheses of two polypeptides demonstrated that the use of the aminomethyl polystyrene resin prepared in this manner was equal to or better than that prepared using the hydrazine method.[6]

2.6. Library applications

Mycobacterium tuberculosis (Mtb) and *Yersinia pestis* (Yp) produce siderophores with scaffolds of nonribosomal peptide–polyketide origin. Compounds with structural similarities to these siderophores have been synthesised and evaluated as antimicrobials against Mtb and Yp under iron-limiting conditions. Several new antimicrobials have been identified, including some with increased potency in the iron-limiting condition. This study illustrates the possibility of screening compound libraries in both iron-rich and iron-limiting conditions to identify antimicrobials that may selectively target iron scarcity-adapted bacteria. It also highlights the usefulness of building combinatorial libraries of compounds having scaffolds with similarities to siderophores to feed into antimicrobial screening programs.[7]

A library of chemokine antagonists has been synthesised using a combination of solid- and solution-phase chemistry. Structures of known chemokine antagonists were used to produce a pharmacophore which served to guide monomer selection. Several combinations of monomers have resulted in providing novel chemokine antagonists which in some cases display dual chemokine receptor antagonism.[8]

A potent, selective lead series that shows antagonism against the human histamine H4 receptor has been discovered from thirteen actives identified in an HTS as part of a hit to lead program. By focusing on ligand efficiency and concurrently using a diversity based approach, active compounds based around 2,4-diaminopyrimidine were identified.[9]

A multicomponent reaction (MCR) approach involving palladium catalysed C–C bond forming reaction has been developed as a new strategy to access systematically modified functionalised 2-aminochromenes. This MCR involves the use of bromobenzaldehyde as a key component and has been exemplified by making a new compound library. Many of these compounds showed *M. tuberculosis* H37Rv chorismate mutase inhibiting properties *in vitro*.[10]

The medicinal chemistry of oral small molecule factor Xa inhibitors has been recently discussed, highlighting key advances that led to clinical candidates and the first licensed medicines. Identification of neutral ligands for the primary specificity pocket was a key discovery; capitalised upon by structure based design and combinatorial methods to deliver many variations on the theme; but it was good medicinal chemistry practice, in the optimisation of physical properties, which ultimately delivered efficacious compounds with adequate oral exposure.[11]

A library of new *N*-Mannich bases derived from 5-cyclopropyl-5-phenyl- and 5-cyclopropyl-5-(4-chlorophenyl)-imidazolidine-2,4-diones have been synthesised. Initial anticonvulsant screening was performed using intraperitoneal (ip), maximal electroshock (MES), and subcutaneous pentylenetetrazole (*sc*PTZ) seizure tests. The *in vivo* results in mice showed that all compounds were effective, especially in the MES screen.[12]

With the non-specific toxicity of anticancer drugs to healthy tissues upon systemic administration, formulations capable of enhanced selectivity in delivery to the tumour mass and cells are highly desirable. A combinatorial-designed strategy where the nano-sized formulations are tailored based on the physicochemical properties of the drug and the delivery needs have been investigated. Individually functionalised C_2 to C_{12} lipid- thiol-, and poly(ethylene glycol)-modified dextran derivatives have been synthesised via 'click' chemistry from *O*-pentynyl dextran and relevant azides. These functionalised dextrans in combination with anticancer drugs form nanoparticles by self-assembling in aqueous medium.[13]

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